24. (new) The method of claim 23, wherein the immunosuppressant compound is deoxyspergualin.

25. (new) The method of claim 23, wherein the immunosuppressant compound blocks IL-12-induced induction of interferon-γ.

26. (new) The method of claim 23, wherein the immunosuppressant is administered beginning from about 0 to 6 hours before the transplanting step.

II. REMARKS

Claims 1-22 are pending in the application and claims 11-21 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 5, 7, and 8 have also been withdrawn from consideration. Claims 1-4, 6, 9, 10, and 22 have been rejected. Applicants respectfully traverse the rejection of claims 1-4, 6, 9, 10, and 22 and amend claims 1 and 22 herein and add new claims 23-26. Support for the new claims can be found in the claims as originally filed.

ELECTION OF SPECIES

Applicants note that the restriction of claims 5, 7, and 8 was maintained. Applicants, however, maintain their traversal because the Applicants believe the genus claim is patentable and the number of species is reasonable.

SEQUENCE LISTING

The sequence listing in this application has been replaced with the sequence listing provided by amendment in the parent application, which includes the sequences for all

sequences in Table 6, as amended. The computer readable form in the instant application is identical with the sequence listing provided by amendment on December 15, 1998, in Application Number 08/737,703, filed October 29, 1996, an application to which the present application claims priority. In accordance with 37 C.F.R. 1.821(e), please use the last filed computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in the application number, filing date, and inventors for the computer readable form that will be used for the instant application.

Table 6 is also amended herein to replace the previous Table 6, which lacked the proper designations of SEQ ID NOs. The new Sequence Listing provided by the previous paragraph includes the new SEQ ID NOs provided with Table 6. Table 6 was similarly amended in the parent application.

CLAIM TO PRIORITY

Applicants amended the specification herein by amending the claim to priority. Applicants believe this addresses the Examiner's objection and makes the claim consistent with the priority claims acknowledged in the Declarations and Powers of Attorney. Applicants, however, are unsure what the Examiner meant by paragraph 4 of the Office Action dated April, 5, 2001, as the Examiner stated she did find support in the 60/015,459 application but indicated that the present application is entitled to a priority date of April 15, 1996 which is the filing date of 60/015,459. As the Examiner seemed to indicate that support could not be found in 60/015,459, Applicants direct the Examiner to at least page 6, lines 11-20, and page 49, line 9, through page 50, line 7, where the sFv-DT390 constructs are discussed. In addition, the Examiner is directed to at least page 5, lines 11-20, page 38, lines 16-22, and page 48, line 1, through page 52, line 26, in the 60/008,104 application where the sFv-DT390 constructs are also discussed and to page 5, lines 18-27 and page 41, line19, through page 42, line 14, in the 08/739,703 application. As the Examiner stated that neither the 08/739,703 application nor the 60/008,104 application was available, copies of each

application and their filing receipts are enclosed. Applicants certify by the signature below that the copies are identical to the provisional application filed on October 30, 1995, and later designated U.S.S.N. 60/008,104, and to the utility application filed on October 29, 1996 and later designated U.S.S.N. 08/739,703. Given the support in these applications, Applicants believe that they are entitled to a priority date of October 30, 1995.

REFERENCES NOT YET CONSIDERED

Enclosed with this Amendment are copies of the references cited in United States patent application 08/739,703 as requested by the Examiner in paragraph 5 of the Office Action dated April 5, 2001. Applicants respectfully request review of these disclosed references and acknowledgement of the same on the PTO-1449 form submitted by the Applicants.

DOUBLE PATENTING

The Office Action dated April 5, 2001 rejected claims 1-4, 6, 9-10, and 22 under the judicially created doctrine of obviousness type double patenting as allegedly being unpatentable over claims 1 and 3-8 of U.S. Patent No. 6,103,235 (the '235 patent) in view of Thompson et al., JBC, 270:28037-41 (1995).

This double patenting rejection, in so far as it is based on the combination of Thompson et al., is overcome, as the application is entitled to the priority date of October 30, 1995, which antedates the Thompson reference from November 24, 1995. The Examiner has indicated, however, that the double patenting rejection would remain over claims 1 and 3-8 regardless of the Thomson reference. Applicants traverse this rejection, for the following reasons.

Obviousness-type double patenting rejections are made when a U.S. patent application by an inventor claims an obvious variation of the invention claimed in another

U.S. application or issued U.S. Patent by the same inventor. The function of the rejection is to prevent an inventor from obtaining more than one patent for the same invention. A proper rejection must consider all limitations of the claims. A rejection for "obviousness-type" double patenting should only be made when there is no "patentable difference" between the claims of the application at issue and the claims of the other application or patent, or, stated another way, the claims in the application are an obvious variation over the claims in the other application or patent. "[A] double patenting of the obviousness type rejection is analogous to [a failure to meet] the non-obviousness requirement of 35 U.S.C. §103, except that the patent principally underlying the double patenting rejection is not considered prior art." *In re Longi*, 759 F.2d 887, 892 n.4. (Fed. Cir. 1985), *citing In re Braithwaite*, 379 F.2d 594, 600 n.4 (C.C.P.A. 1967) ("While analogous to the non-obviousness requirement of 35 U.S.C. §103, that section is not itself involved in double patenting rejections because the patent principally underlying the rejection is not prior art.")

A proper double patenting rejection must consider the **claim** as a whole, including all limitations. *General Foods Corp. v. Studiengesellschaft Kohle*, 972 F.2d 1272, 1283 (Fed. Cir. 1992) ; *Carman v. Wahl*, 724 F.2d 932, 940 (Fed. Cir. 1983); *cf.* Ex Parte Crissy, 201 U.S.P.Q. (BNA) 689, 693 (Pat. Off. Bd. App. 1976). "[T]he *disclosure* of a patent cited . . . cannot be used as though it were prior art, *even where the disclosure is found in the claims.*" *General Foods*, 972 F.2d at 1281. One must assess whether the claims of the cited patent are directed to the subject matter of the contested claims, not whether the words of the cited claims, when used as a prior art reference, make obvious the contested claims. *In re Sarett*, 327 F.2d 1005, 1013 (C.C.P.A. 1964). The court stated, "We are not here concerned with what one skilled in the art would be aware from *reading* the claims but with *what inventions the claims define." Id.* at 1013. This means that the standard of obviousness-type double patenting is a comparison of the *inventions* as defined by the claims.

Claim 1 of the '235 patent reads as follows:

> A method of inhibiting a rejection response in a primate recipient, by inducing immune tolerance in the primate recipient, to foreign mammalian donor cells, tissue or organ, comprising the steps of:

a) exposing the recipient to an anti-CD3-DT immunotoxin with reduced anti-DT antibody binding so as to reduce the recipient's T-cell lymphocyte population by at least 80% in the presence or absence of anti-DT antibodies in the recipient; and

b) transplanting the donor cells, tissue or organ, into the recipient, such that a rejection response by the recipient to the donor cell, tissue or organ, is inhibited.

Nothing in claim 1 or in claims 2-8 of the issued patent recites sFv-390. It is axiomatic that the obviousness type double patenting rejection must be based on the claims and cannot rely on the non-claim disclosure or other disclosures to supplement the obviousness rejection. See Donald S. Chisum, Chisum on Patents § 9.03 ("[In the context of double patenting, t]he standard for comparison for the second patent is what was claimed in the first patent, not what was disclosed in the specification of the first patent.") (collecting cases).

In re Kaplan, 789 F.2d 1574 (Fed. Cir. 1986), has facts very similar to the present case. In that case, the issued patent was directed to a genus claim (a method of making a chemical in the presence of an organic solvent), and the pending application, which was rejected under the doctrine of double patenting, claimed a species (a method of making the chemical in the presence of a combination of organic solvents). The species was disclosed but unclaimed in the issued patent. The *Kaplan* court reversed the double patenting rejection and stated that "the patent disclosure may not be used as prior art." A genus cannot make obvious a particular species contained within the genus. While the claims of the '235 patent cover the present claim, they do not make obvious the present species claim. Nothing within the issued claims suggests or would motivate one of skill in the art to focus on the particular immunotoxin, sFv-DT390. Therefore, claims 1, and 3-8 cannot make claims 1-4, 6, 9-10, and 22 obvious.

In re Schneller, 397 F.2d 350 (C.C.P.A. 1968), which was cited by the Examiner, can be distinguished from the present case. The *Schneller* case was a pre-GATT case (i.e., prior to 1995), and patent term at that time was 17 years from the date of issuance of a patent. Even though the application at issue in *Schneller* claimed priority to the issued patent that gave rise to the double patent objection, the new claims if issued in that case would have substantially extended the patent term. Such is not the case now. As amended in 1994, 35 U.S.C.§ 154, provides that the patent term ends "20 years from the date on which the application for the patent was filed in the United States, or, if the application or applications under section 120, 121, or 365(c) of this title, from the date on which the earliest such application was filed." Thus, the term of the instant application cannot extend past twenty years from the earliest claimed priority date of the application filed from the first provisional application (i.e., the filing date of the 08/739,703 application), which is October 29,1996. The parent '235 application has the same term. Thus, the *Schneller* court's concern regarding patent term is not proper in the present case. Applicants respectfully traverse this obviousness type double patenting rejection.

35 U.S.C. § 112, ¶ 1

The Office Action dated April 5, 2001, rejected claims 1-4, 6, 9-10, and 22 under 35 U.S.C. § 112, ¶ 1, for allegedly failing to provide an adequate written description of the invention and failing to provide an enabling disclosure. In paragraph 10 on pages 8-11 of the Office Action, it appears that the Examiner believes that the specification does not teach how to make and use an immunotoxin having the sFv-DT390 construct because the sFv-DT390

construct has not been deposited and the sequence of sFv-DT390 is not disclosed in the application.

Reproduced below for the Examiner's convenience is a section of the present application (page 50, line 4 to page 51, line 1) in which the making of sFv-DT390 is fully disclosed. This section can also be found in the priority application 60/008,104 at page 40,line 18 to page 41, line 13. This section clearly indicates that one of skill in the art could make the appropriate reagents to practice the claimed methods.

> The recombinant immunotoxin, sFv-DT390, was generated in two phases. First the coding sequences for the variable light (V_L) and variable heavy (V_H) chain regions of the UCHT1 antibody were amplified by a two step protocol of RT-PCR using primers based on the published sequence (13). The 5′ V_L primer added a unique NcoI restriction enzyme site while the 3′ V_H primer added a termination codon at the J to constant region junction and an EcoRI site. The V_L region was joined to the V_H region by single-stranded overlap extension and the two regions are separated by a $(Gly_3Ser)_4$ linker that should allow for proper folding of the individual variable domains to form a function antibody binding site (14). Second, genomic DNA was isolated from a strain of *C. diphtheriae* producing the DT mutant CRM9 (C7[$\beta^{tox\text{-}201tox\text{-}9h'}$]) as described (15). This DNA was used for PCR. The 5′ primer was specific for the toxin gene beginning at the signal sequence and added a unique NdeI restriction site. The 3′ primer was specific for the DT sequence terminating at amino acid 390 and added an NcoI site in frame with the coding sequence. The PCR products were digested with the appropriate restriction enzymes and cloned into the *E. coli* expression plasmid pET-17b (Novagen, Inc., Madison, WI, USA) which had been linearized with NdeI and EcoRI. The resulting plasmid was used to transformed *E. coli* BL21/DE3 cells. Cells were grown to an OD_{590} of 0.5, induced with 0.5 M IPTG (Invitrogen, San Diego, CA, USA) and incubated for an additional 3 hours. The sFv-DT390 protein was isolated in the soluble fraction after cells were broken with a French Press and the lysate subjected to centrifugation at 35,000 X g.

Thus, it is clear from the specification that the specific protocol needed to make the sFv-DT390 construct was outlined in the specification and all of the reagents needed to perform these operations were obtainable. Thus, the Applicants respectfully traverse this rejection.

Since the specification teaches how to make the sFv-DT390 as indicated above and discussed in the Office Action dated April 5, 2001, (page 8-9), Applicants understand the main concern of the Examiner to be that, "it does not appear that all restrictions upon public access to the antibody [UCTH-1] have been irrevocably removed or that viable samples of the antibody will be made available for the life of any patent issued." Applicants point the Examiner to Table 1 of the application, which indicates that UCTH-1 can be purchased from Oxoid USA, Inc. Clearly, since one can purchase the needed reagents, the Examiner's concerns have been addressed. In addition, should the Examiner require more, it is equally clear to one of ordinary skill in the art how to derive nucleic acid encoding UCHT1 through synthetic means given the sequence of UCHT1 (obtainable from Shalaby MR, et al., "Development of humanized bispecific antibodies reactive with cytotoxic lymphocytes and tumor cells overexpressing the HER2 protooncogene," J Exp Med. 175(1):217-25 (1992)). This is the publication cited in the reproduced section from the specification cited above. Thus, Applicants respectfully traverse this rejection in light of the arguments provided above.

The Examiner also objects to the language in claim 1, "inducing immune tolerance." Applicants amend claim 1 herein to facilitate prosecution. Specifically, the phrase "by inducing immune tolerance" has been deleted from the preamble as unnecessary language. This amendment is not a narrowing amendment.

35 U.S.C. § 112, ¶ 2

The Examiner objects, under 35 U.S.C. § 112, 2d paragraph, to the phrase "sFv-DT390" as rendering claims 1-4, 6, 9-10, and 22 indefinite. The previous section of this response, however, provides detail about how the sFv-DT390 was made and what it comprises. One skilled in the art, given the definition and description provided in the specification, would readily understand the designation "sFv-DT390." Applicants, thus, traverse the rejection.

The Examiner also rejects the same claims on the same grounds because of the phrase "to reduce T-cell lymphocyte population by at least 80%." Applicants have amended claim 1 to clarify that the reduction in the recipient's T-cell lymphocyte population is as compared to the recipient's T-cell lymphocyte population prior to administration of the immunotoxin. Support for this amendment can be found on page 21, which states that "[t]he preferred doses of the immunotoxin are those sufficient to deplete peripheral blood T-cell levels to 80% . . . of preinjection levels." No new matter is believed to be added, and Applicants request withdrawal of the rejection in view of the amendment.

The Examiner rejects the same claims under § 112, 2d paragraph, because of the phrase "exposing the recipient to." Applicants have amended claim 1 to recite "administering to the recipient." Support can be found throughout the specification, including, for example, page 4, line 8, and now new matter is added. Applicants request withdrawal of the rejection.

Claim 22 is also rejected under §112, 2d paragraph, because "said immunosuppressant" allegedly lacks antecedent basis in claim 1. Claim 22 has been amended to depend on claim 6, which properly provides such antecedent basis.

35 U.S.C. § 103

Claims 1-4 are rejected under 35 U.S.C. § 103 as allegedly obvious based on Thompson et al., in view of U.S. Patent No. 5,725, 857; claims 1-4, 6. 9-10, and 22 are rejected under 35 U.S.C. § 103 as allegedly obvious based on the same references and further in view of Lu et al. (J. Amer. Soc. Nephrol. 4:1239-1256). As discussed above, however, the present claims have priority to October 1995, which predates the Thompson et al. reference, thereby eliminating Thompson et al. as prior art to this claimed invention. Applicants accordingly request reconsideration and withdrawal of this rejection, as neither of the other references standing alone can render the claims obvious.

ATTORNEY DOCKET NO. 14028.0292
Serial No. 09/383,695

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending claims are believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of the application to issue.

No fee is believed to be due; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence and anything indicated as included with this correspondence is being transmitted via Facsimile No. 703-308-4242, addressed to: Examiner S. Ungar, Group Art Unit 1642, U.S. Patent and Trademark Office, on the date shown below.

Tina Williams McKeon — December 27, 2001
Date

Appendix A

Marked-Up Version to Show Amendments

In the Specification

Page 1, first paragraph, before "Background of the Invention":

This application [is a divisional of, and claims the benefit of, application serial No. 08/843,409, filed April 15, 1997, which status is pending, which application is hereby incorporated herein by reference. This application for letters patent claim priority under 35 U.S.C. § 119(e) of provisional patent application serial number 60/015,459, filed on April 15, 1996, now abandoned, having the same title of invention and the same inventors as the present application. This application also claims priority to U.S. Serial No. 08/739,703, filed October 29, 1996.] is a continuation of and claims priority to U.S.S.N. 08/843,409, filed April 15, 1997, now U.S. Patent No. 6,103,235, which is incorporated herein by reference in its entirety and which is a continuation-in-part of U.S.S.N. 08/739,703 filed October 29, 1996, now abandoned, and claims priority to U.S. Provisional Patent Application Serial Number 60/015,459, filed April 15, 1996, now abandoned, and U.S. Provisional Patent Application Serial Number 60/008,104, filed October 30, 1995, 1998, all of which are incorporated herein by reference.

On page 67:

Table 6. Sequences of oligonucleotide primers used for PCR amplification

Sequence ID Number	Sequence 5' 3'	Primers	RE sites
SEQ ID NO. 7	GACATCCAGATGACCCAGACC	P1 (UCHT1 VL5)	
SEQ ID NO. 8	CCTCCCGAGCCACCGCCTCCGCTGCCTCCGCCTCCTTTTA TCTCCAGCTTG(T)GTC(G)CC	P2 (UCHT1 VL3)	
SEQ ID NO. 9	GCAGCGGAGGCGGTGGCTCGGGAGGGGGAGGCTCGGAGGT GCAGCTTCAGCAGTCT	P3 (UCHT1 VL5)	
SEQ ID NO. 10	GC**AAGCTT**GAAGACTGTGAGAGTGGTGCCTTG	P4 (UCHT1 VH3)	Hind III
SEQ ID NO. 11	GTCTCTTCA**AAGCTT**ATTGCC(T)GAGCTGCCTCCCAAA	P5 (HuIgM-CH2)	Hind III
SEQ ID NO. 12	GCA**TCTAGA**TCAGTAGCAGGTGCCAGCTGTGT	P6 (HuIgM-CH4)	Xba I
SEQ ID NO. 13	CG**GTCGAC**ACCATGGAGACAGACACACTCCTGTTATGGGT ACTGCTGCTCTGGGTTCCA	SP1 (*signal seq1*)	Sal I
SEQ ID NO. 14	GTACTGCTGCTCTGGGTTCCAGGTTCCACTGGGGACATCC AGATGACCCAG	SP2 (*signal seq2*)	

RE: restriction enzyme.
Restriction sites appeared in the primers were underlined and bold.
The primers listed as SEQ ID NO:8 and SEQ ID NO:11 consisted of a mixture of the sequence without the nucleotide(s) in parentheses and the sequence (s) with the nucleotide(s) in parentheses replacing the immediately preceding nucleotide(s) in the sequence.

DEC. 27. 2001 5:15PM NEEDLE & ROSENBERG NO. 913 P. 17

On pages 104-106, the last filed Sequence Listing in the parent application is incorporated therefor.

In the Claims

Amended claims 1 and 22 are provided:

1. A method of inhibiting a rejection response in a primate recipient[, by inducing immune tolerance] to foreign mammalian donor cells, tissue or organ, comprising the steps of:

   a) administering to [exposing] the recipient [to] an anti-CD3-DT immunotoxin, wherein the immunotoxin comprises sFv-DT390, so as to reduce the recipient[s]'s T-cell lymphocyte population by at least 80%, as compared to the recipient's T-cell lymphocyte population prior to administration of the immunotoxin; and

   c) transplanting the donor cells, tissue or organ, into the recipient, such that a rejection response by the recipient to the donor cells, tissue or organ, is inhibited.

22. The method of claim 6 [1], wherein the immunosuppressant is administered beginning from about 0 to 6 hours before the transplanting step.

New claims 23-26 as provided:

23. A method of inhibiting a rejection response in a primate recipient, by inducing immune tolerance to foreign mammalian donor cells, tissue or organ, comprising the steps of:

   a) administering to the recipient an anti-CD3-DT immunotoxin, wherein the immunotoxin comprises sFv-DT390, so as to reduce the recipients's T-cell lymphocyte population by at least 80%, as compared to the recipient's T-cell lymphocyte population prior to administration of the immunotoxin;

   d) administering an immunosuppressant compound to enhance the anti-T cell effects of the immunotoxin; and

   e) transplanting the donor cells, tissue or organ, into the recipient, such that a rejection response by the recipient to the donor cells, tissue or organ, is inhibited.

24. The method of claim 23, wherein the immunosuppressant compound is deoxyspergualin.

25. The method of claim 23, wherein the immunosuppressant compound blocks IL-12-induced induction of interferon-γ.

26. The method of claim 23, wherein the immunosuppressant is administered beginning from about 0 to 6 hours before the transplanting step.